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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,592	12/11/2003	Arthur M. Krieg	C 1037.70038US01	2533

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
03/19/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/735,592	KRIEG ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/5/07, 10/22/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-37,52,63-65,68,69,75 and 90* is/are pending in the application.

4a) Of the above claim(s) *2-5,11-16,20-22,25-27,52,63-65,68,69 and 75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-8,10,17-19,23,24 and 90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *See Continuation Sheet* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/15/08, 6/16/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 2-5,11-16,20-22,25-37,52,63-65,68,69 and 75.

DETAILED ACTION

Response to Amendment

1. Applicants' amendments filed July 5, 2007 and October 22, 2007 are acknowledged and have been entered. Claims 9, 38-51, 53-62, 66, 67, 70-74 and 76-89 have been canceled. New claim 90 has been added. Claims 1-8, 10-37, 52, 63-65, 68, 69, 75 and 90 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.

2. Claims 2-5, 11-16, 20-22, 25-37, 52, 63-65, 68, 69 and 75 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 27, 2006.

3. Claims 1, 6-8, 10, 17-19, 23, 24 and 90 have been examined in the pending application.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 6-8, 10, 17-19 and 90 are rejected under 35 U.S.C. 102(b) as being anticipated by Klinman et al (WO 00/61151; publication date Oct. 19, 2000).

The prior art discloses oligonucleotides comprising the formula, 5'TCG$X_1X_2N_13$', as set forth in claim 1. Klinman et al discloses SEQ ID NO: 5 (tcgactctcgagcgttctc) that would be encompassed in the above formula. (see attached pages from WO 00/61151). These sequences do not have an unmethylated CG motif in N_1 (pending claim 1). The sequences include at least one modified internucleotide linkage, Klinman et al at p. 18 (pending claims 6-8 and 10). The oligonucleotides of Klinman et al disclose that the oligonucleotide can be 13-100 nucleotides in length, see p. 3; p. 18 (pending claims 1, 90). The oligonucleotides of Klinman et al disclose at least 50% and at least 80% pyrimidine (pending claims 17 and 18). The oligonucleotides of Klinman et al disclose that N_1 is free of Poly-A and Poly-G sequences (pending claim19). The prior are anticipated the claimed invention.

Since the Patent Office does not have the facilities for examining and comparing applicants' oligonucleotides with the oligonucleotides of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed oligonucleotides and the oligonucleotides of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's arguments filed July 5, 2007 have been fully considered but they are not persuasive. "Applicants have amended Claim 1 to add the limitation that the oligonucleotide is 13-100 nucleotides in length. Although some of the general language cited in Klinman et al suggest that oligonucleotides can have lengths up

to 100 nucleotides, there is no teaching that the oligonucleotides of SEQ ID NO: 117, 119, 120, 133 and 135 have a length between 13 and 100 nucleotides. In fact each has a specified length of 12 nucleotides according to the sequence listing. New claim 90 includes the limitation that the oligonucleotide has a length of 13-40 nucleotides. Therefore, the rejection under 35 U.S.C. 102(b) in view of Klinman et al. (WO 00/61151) should be withdrawn and is not applicable to new claim 90." (see Remarks, p. 13)

Although Applicants have amended the instant claims to recite that the oligonucleotide is 13-100 nucleotides in length or 13-40 nucleotides in length, the prior art of Klinman et al discloses the claimed invention as set forth above. The oligonucleotides of Klinman et al disclose that the oligonucleotide can be 13-100 or 13-40 nucleotides in length, see p. 3, l. 16-25. Klinman et al specifically discloses oligonucleotides 100 nucleotides or less—10-75; 50 nucleotides or less—10-40; 30 nucleotides or less—10-20 and 12-16 nucleotides.

6. Claims 1, 6-8, 10, 17-19 and 90 are rejected under 35 U.S.C. 102(b) as being anticipated by Peterson et al (WO 95/03407; publication date February 2, 1995).

The prior art discloses oligonucleotides comprising the formula, 5'$TCGX_1X_2N_1$3', as set forth in claim 1. Peterson et al discloses SEQ ID NO: 11 (TCGCCGCCCC TCGCCTCTTG CCGTGC) and SEQ ID NO: 27 (TCGGGCCTGTCGGGTCCCCTCG) that would be encompassed in the above formula (see p. 9). These sequences do not have an unmethylated CG motif in N_1 (pending claim 1). The sequences include at least one modified internucleotide linkage, see Peterson et al at p. 13 (pending claims 6-8 and 10). The oligonucleotides of Peterson et al disclose that the oligonucleotide can be 13-100

nucleotides in length, see p. 14 as well as sequences above (pending claims 1, 90). The oligonucleotides of Peterson et al disclose at least 50% and at least 80% pyrimidine (pending claims 17 and 18). The oligonucleotides of Peterson et al disclose that N_1 is free of Poly-A and Poly-G sequences (pending claim19). The prior are anticipated the claimed invention.

Since the Patent Office does not have the facilities for examining and comparing applicants' oligonucleotides with the oligonucleotides of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed oligonucleotides and the oligonucleotides of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 6-8, 10, 17-19, 23, 24 and 90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 is directed to an oligonucleotide comprising: 5'$TCGX_1X_2N_1$3' wherein X_1 is any nucleotide, X_2 is A, T, or C when X_1 is C or A, X_2 is A or G when X_1 is T, X_2 is any nucleotide when X_1 is G, N_1 is 2-95 nucleotides, wherein 5' designates the 5' end of the oligonucleotide and 3' designates the 3' end of the

oligonucleotide, and wherein N_1 does not include an unmethylated CG motif, wherein the oligonucleotide is 13-100 nucleotides in length.

The claims do not indicate that any CG motif in the oligonucleotide is unmethylated. Further, the claims do not set forth any function for the claimed oligonucleotides. The specification, at p. 2, l. 17-20, indicates, "The invention involves the finding that specific sub-classes of CpG immunostimulatory oligonucleotides having a 5'CpG are highly effective in mediating immune stimulatory effects. These CpG nucleic acids are useful therapeutically and prophylactically for stimulating the immune system to treat cancer, infectious diseases, allergy, asthma and other disorders and to help protect against opportunistic infections following cancer chemotherapy. The strong yet balanced, cellular and humoral immune responses that result from CpG stimulation reflect the body's own natural defense system against invading pathogens and cancerous cells." And that "oligonucleotides having a '5TCG motif without any additional unmethylated CpG motifs have strong immunostimulatory capability." (p. 2, l, 25-26)

The state of the art teaches that the unmethylated CpG in these immunostimulatory sequences are responsible for the immune stimulatory activity in view of the fact that when these motifs are methylated the activity is lost (Krieg, Trends in Microbiology, June 2001, 9/8:249-252; see also Verthelyi et al, Clinical Immunology, 2003, 109:64-71). Lin et al (J. Invest. Medicine, September 1997, 45/7:333A abstract only) teaches that oligodeoxynucleotides containing unmethylated CpG dinucleotides are capable of inducing activation of cells including B cell and monocytes/macrophages that participate in antigen presentation.

In view of all of the above it would require undue experimentation to practice the claimed invention. Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to the claimed oligonucleotide, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). With regard to (4) the nature of the invention and (5) the state of the prior art, these have been discussed above. One of skill in the art would require guidance, in order to make or use the oligonucleotide as claimed. For reasons stated above (i.e. lack of enabling disclosure, unpredictability of the art, and lack of guidance) it would require undue experimentation to practice the claimed invention. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In view of all of the above, the pending specification does not enable the claimed invention and therefore the pending claims are not enabled.

9. No claims are allowed.

10 .Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/N. M. Minnifield/
Primary Examiner, Art Unit 1645
March 12, 2009